Pain therapy with oxycodone/naloxone prolonged-release combination: case report

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Pain afflicts patients suffering from many chronic diseases and is present in 80% of cases of patients with advanced cancer who suffer from persistent pain. The aim of the pain treatment is to achieve the maximum analgesic effect while minimizing side effects. The main analgesic agent – morphine is unfortunately a therapy associated with gastrointestinal side effects. It appears that the combination of oxycodone and naloxone available as Targin® (Mundipharma) is an alternative. The paper presents a case of a 45-year-old patient who was treated effectively with oxycodone/naloxone prolonged-release tablets. This treatment has proven to be effective in providing pain and constipation control.

Key words: pain, constipation, opioids, oxycodone/naloxone.

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Introduction

Pain is a sensory and physical sensation associated with tissue damage. A characteristic feature of pain is a sensation which enables the location and response to perceived pain stimulus. The primary functions of pain in the body are its warning and protective effects.

It is assumed that chronic pain is pain lasting longer than 3 months and affects 30% of patients diagnosed with cancer and about 70–80% of patients with advanced cancer [1–4]. In the EPIC (European Pain in Cancer) study 66–67% of patients identified pain associated with cancer as very stressful and significantly affecting their professional activity and social life. It should be noted that pain is responsible for the need to resign from work or limit professional activity and decreases the quality of work performed by an active employee. The basis of analgesic therapy is the three-step analgesic ladder on the top of which are the drugs belonging to the group of strong opioids. Opioids are the basis of treatment of moderate to severe pain. About 60% of patients in the USA and about 43% in Europe have used weak or strong opioids for pain control [2–11].

It was demonstrated that opioids act effectively as analgesics but they also cause a number of side effects, among which the most common is constipation. They concern 40–80% of patients treated with opioids and the risk of occurrence increases further in patients with end-stage cancer [5, 12, 13]. Constipation is not a disease entity, but a symptom. The Working Group of the Polish Society of Palliative Medicine in the recommendations entitled "Therapeutic management of patients with constipation in palliative care" defined constipation as a decreased frequency of bowel movements (to less than 3 per week) or subjective patient's complaints, such as: difficulty in defecation, hard stools, straining or incomplete bowel movements [14]. Opioid-induced constipation is part of a broader syndrome – opioid-induced bowel dysfunction (OIBD). It results from the mode of action of these drugs. On the one hand, it is caused by activation of opioid receptors in neurons of the spinal cord that results in a slowdown of intestinal transit and reduced secretory function [15–17]. On the other hand, it is caused by the effects of opioids on the enteric autonomic nervous system (ENS). It functions independently of the central nervous system with the involvement of Auerbach's plexus and Meissner's plexus, which are responsible for the motility of the intestine. Inhibition of peristalsis is regulated by the activation of κ and μ receptors, while the δ receptor does not participate in this mechanism [18–22]. Opioids act by inhibiting kinetics of the stomach and propulsion of the small intestine resulting in prolongation of gastrocaecal transit time. Dry faecal masses form in the intestinal lumen due to increased water absorption. Rectal sensitivity to stretching decreases while the tension of rectal sphincter increases [17, 21, 23, 24].

The OIBD should be recognized as the cause of constipation regardless of the co-occurrence of risk factors such as general condition, conditions of care, dietary factors, mechanical or functional obstacles in the digestive system, metabolic and hormonal disorders, and neurological or psychiatric disease.

The OIBD syndrome is accompanied by discomfort and pain in the abdomen as well as gastro-oesophageal reflux. With the use of opioids to prevent adverse effects mentioned above it is necessary to use prophylactic administration of laxatives [22, 24, 25]. The European data show that 25% of patients do not receive a prescription for such medication, and only a small proportion of them decide to buy these drugs without a prescription [5].

Constipation significantly decreases the quality of life, making effective pain control difficult. In a study conducted in Sweden it was demonstrated that the degree of satisfaction with analgesic therapy and quality of life of patients show a negative correlation with the degree of severity of the OIBD symptoms [26]. Constipation is the most important and most common adverse event observed in the opioid therapy [13, 20, 21]. Economic analyses evaluating differences in the cost of treatment of patients suffering from OIBD and patients free from this syndrome showed a higher cost of therapy of patients suffering from OIBD. Patients with OIBD require more attention from the medical staff and are more often hospitalized, and the cost of palliative care is increased [17, 23, 27].

Case study

The study concerns a 45-year-old man, treated in an Outpatient Palliative Care Clinic because of cancer pain in the abdominal cavity with radiation of pain to the area of the sacro-lumbar spine (visceral pain with neuropathic component). When taken to hospital the patient was experiencing breakthrough pain (NRS scale 8–9), vomiting, no pain control as well as weaken of bowel prokinetic, constipation and lack of appetite

Due to obstructive jaundice the patient had a CT of the abdominal cavity and the small pelvis. No pathological lesions were detected in the imaging. Therefore it was decided to perform surgery, which was done in March 2011. During exploratory laparotomy an inoperable tumour of the pancreas was found. A biopsy of the pancreas and biliary stenting were performed. Histopathological examination did not confirm the proliferative process. The patient was taking ketoprofen 50 mg on an *ad hoc* basis for pain in the upper abdomen.

In view of the reported pain a decision was made to perform an abdominal CT scan, which was done in August 2011. The exam revealed a tumour of the head of the pancreas reaching to the root of the mesentery, causing infiltration of the duodenum, enlarged lymph nodes in the retroperitoneal space and metastases in both lobes of the liver.

The patient complained of pain of a severity 5–6 on the NRS scale. It was decided to include tramadol at a dose of 200 mg/day in the treatment. A good control of the pain was achieved, due to tramadol, with the severity of 2–3 on the NRS scale. The patient used ketoprofen at a dose of 50 mg on an *ad hoc* basis.

In September 2011 the patient underwent another operation because of obstruction of gastrointestinal tract. Gastro-intestinal and gastrointestinal-intestinal anastomosis were performed, and specimens of liver metastases were collected. The result of histopathological examination confirmed malignancy. In view of the good general condition of the patient and normal values of the laboratory parameters, oncological treatment was included. The patient received gemcitabine starting from October 2011. The pain was well controlled with tramadol 200 mg/day and the patient used ketoprofen at a dose of 50 mg on an *ad hoc* basis.

In the course of the chemotherapy disease progression occurred. The imaging studies (ultrasound and computed tomography of the abdominal cavity) confirmed progression of the metastatic disease in the liver. In addition, there was an elevated concentration of the tumour marker, CA19-9 antigen – 2855.00 U/ml (0.00–37.00). In October 2011 the patient was referred to the Outpatient Palliative Care Clinic due to the pain in the upper abdomen that radiated to the area of the lumbar spine. At the same time another line of cancer treatment was included; erlotinib – an inhibitor of the tyrosine kinase receptor for the receptor of the epidermal growth factor (EGFR). On admission to the Outpatient Palliative Care Clinic the patient reported a strong breakthrough pain (8–9 on the NRS scale), vomiting, positive symptoms of psychosis, lack of control of background pain, weakness, impaired intestinal motility – constipation, nausea and vomiting, and loss of appetite. The GP prescribed transdermal fentanyl 25 μg/h, NSAIDs and lactulose. In the Outpatient Palliative Care Clinic subcutaneous morphine was prescribed, at a dose of 20 mg. Once the analgesic effect was obtained, taking into account the need for the use of opioids, with constipation present, a recommendation was made to use a combination of oxycodone + naloxone (Targin) prolonged-release 2 × 10 mg, and fentanyl for breakthrough pain (the buccal tablet) 100 mg on an *ad hoc* basis.

During another visit to the Outpatient Palliative Care Clinic which took place a week later, significant improvement in well-being was recorded. The pain decreased (NRS 5–6). After treatment with Targin®, constipation, nausea and vomiting disappeared and also the appetite improved. Ketoprofen was discontinued. The recommendation was: Targin® (20 mg oxycodone/10 mg naloxone), fentanyl (buccal tablet) 200 μg on an *ad hoc* basis.

After another week of taking Targin® while evaluating the effectiveness of treatment, further, good control of pain and normal and regular bowel movements were recorded. Nausea did not reoccur. The patient noted mood improvement and sustained improvement in appetite. There were no serious side effects of the treatment. Tolerance of the treatment was good.

Summary

In the case study described above pain therapy was applied in accordance with the principles of pain management according to the World Health Organization (WHO). The patient was treated in the first phase with a drug from the group of non-steroidal anti-inflammatory drugs (NSAIDs), which was not the right choice, taking into account the presence of a neuropathic component and the course and diagnosis of the disease. The patient did not use adjunctive treatment with a medication belonging to the group of tricyclic antidepressants or anticonvulsants. In the second stage of symptomatic treatment tramadol was used which has a dual mode of action – it is a weak opioid at the second level of the anal-

gesic ladder and an antagonist of the NMDA receptor complex. Unfortunately, the patient experienced severe constipation and obstruction. The patient complained about a feeling of fullness in the abdomen reported two bowel movements per week and after defecation there was a sensation of stool retention that could be potentially life-threatening in case of obstruction. The use of oxycodone-naloxone prolonged-release combination was a good choice due to the analgesic effect of oxycodone and the impact on normalization of gastrointestinal function by the opioid antagonist – naloxone. Upon oral administration, naloxone prevents binding of oxycodone with receptors in the gut wall, before the two substances reach the liver where approximately 97% of naloxone is metabolized. 50% to 80% of oxycodone reaches the systemic circulation causing analgesia.

The use of oxycodone-naloxone combination in the form of Targin® in the case of a 45-year-old patient turned out to be an effective solution in the treatment of a mixed pain with nociceptive and neuropathic components. In addition, the use of oxycodone-naloxone combination has been shown to act against constipation, with a minimal emetic effect that is typical for other opioids.

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